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**Acute Oral Toxicity of
Methyl-N,N'-dihexylethylene diaminemonocarbamate
(CHR4) in Sprague-Dawley Rats**

*Gerald F.S. Hiatt, PhD
Max Goldman, PhD
and
Don W. Korte, Jr., PhD, LTC, MSC*

MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

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DONALD R. CORBY

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22a. NAME OF RESPONSIBLE INDIVIDUAL DONALD G. CORBY, COL, MC		22b. TELEPHONE (Include Area Code) (415) 561-3600	22c. OFFICE SYMBOL SGRD-ULZ

ABSTRACT

The acute oral toxicity of methyl-N,N'-dihexylethylene diaminemonocarbamate (CHR4) was determined in male and female albino Sprague-Dawley rats administered a single dose by oral gavage. The median lethal doses (MLD) were 261 mg/kg in male and 251 mg/kg in female rats. The spectrum of observed clinical signs and their rapid onset were consistent with CHR4-induced cholinesterase inhibition. The signs included diarrhea, salivation, lacrimation, muscle weakness, changes in reflexes, convulsions, and disorientation. Lethality was observed only within the first eight hours after dosing and toxic signs were observed primarily within the first 24 hours after dosing. These results place CHR4 in the moderately toxic category.

Key Words: Acute Oral Toxicity, CHR4, Insect Repellant, Rat, Methyl-N,N'-dihexylethylene diaminemonocarbamate

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PREFACE

TYPE REPORT: Acute Oral Toxicity GLP Study Report

TESTING FACILITY:

US Army Medical Research and Development Command
Letterman Army Institute of Research
Division of Research Support
Presidio of San Francisco, CA 94129-6800

SPONSOR:

US Army Medical Research and Development Command
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Presidio of San Francisco, CA 94129-6800

PROJECT/WORK UNIT/APC: 3M162770A871, Development of
Repellents Against Medically Important
Arthropods/Work Unit 201/APC: TL01

GLP STUDY NUMBER: 84023

STUDY DIRECTOR: LTC Don W. Korte, Jr, PhD, MSC
Diplomate, American Board of Toxicology

PRINCIPAL INVESTIGATOR: Gerald F. S. Hiatt, PhD

CO-PRINCIPAL INVESTIGATOR: Max Goldman, PhD

PATHOLOGIST: LTC Lance O. Lollini, DVM, VC, Diplomate,
American College of Veterinary Pathologists

REPORT AND DATA MANAGEMENT: A copy of the final report, study
protocols, raw data, SOPs and an
aliquot of the test compound will
be retained in the LAIR Archives.

TEST SUBSTANCE: Methyl-N,N'-dihexylethylene diaminemono-
carbamate (CHR4)

INCLUSIVE STUDY DATES: 7 June - 11 July 1984

OBJECTIVE: To determine the acute oral toxicity of Methyl-
N,N'-dihexylethylene diaminemonocarbamate (CHR4)
in Sprague-Dawley rats.

ACKNOWLEDGMENTS

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**SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS
INVOLVED IN THE STUDY**

We, the undersigned, declare that GLP Study 84023 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte 27 Nov 90 *Don W. Korte* 27 Nov 90
DON W. KORTE JR., PhD / DATE GERALD F.S.HIATT, PhD / DATE
LTC, MS DAC
Study Director Principal Investigator

Carolyn M. Lewis 5 Dec 90 *Don W. Korte* 27 Nov 90
CAROLYN M. LEWIS, MS / DATE MAX GOLDMAN, PhD / DATE
DAC DAC
Data Manager Co-Principal Investigator

Conrad Wheeler 29 Nov 90
CONRAD R. WHEELER, PhD / DATE
DAC
Analytical Chemist



DEPARTMENT OF THE ARMY

LETTERMAN ARMY INSTITUTE OF RESEARCH
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REPLY TO
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28 November 1990

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 84023

1. This is to certify that in relation to LAIR GLP Study 84023 the following inspections were made:

12 June 1984	- Protocol Review
22 June 1984	- Dosing
28 June 1984	- Dosing

2. The institute report entitled "Acute Oral Toxicity of Methyl-N,N'-Dihexylethylene Diaminemonocarbamate (CHR4) in Sprague-Dawley Rats," Toxicology Series 83, was audited on 31 November 1990.

Walter G. Bell

WALTER G. BELL
SFC, USA
Quality Assurance Officer

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**Acute Oral Toxicity of Methyl-N,N'-dihexylethylene diaminemonocarbamate (CHR4) in Sprague-Dawley Rats--
Hiatt et al.**

INTRODUCTION

The goal of the insect repellent program is to develop better insect repellents for the protection of soldiers from insects and insect-borne diseases in the field. The Division of Cutaneous Hazards, Letterman Army Institute of Research (LAIR), has tested a large number of candidate insect repellents submitted by SRI International, the US Department of Agriculture (USDA), and private industry against a variety of mosquitoes, sand flies, fleas, ticks, and mites in both *in vitro* and *in vivo* test systems. Several of the candidate repellents have shown sufficient repellent activity and persistence on the skin of animals to warrant consideration as a replacement for N,N-diethyl-*m*-toluamide (DEET), the active ingredient in the troop-issue insect repellent. One of these new formulations, methyl-N,N'-dihexylethylene diaminemonocarbamate (CHR4), has proven to be an extremely effective repellent (1-4), and thus was submitted to the Division of Toxicology, LAIR, for preclinical toxicity testing.

Objective of the Study

The objective of this study was to determine the acute oral toxicity of methyl-N,N'-dihexylethylene diaminemonocarbamate (CHR4) in Sprague-Dawley rats.

MATERIALS

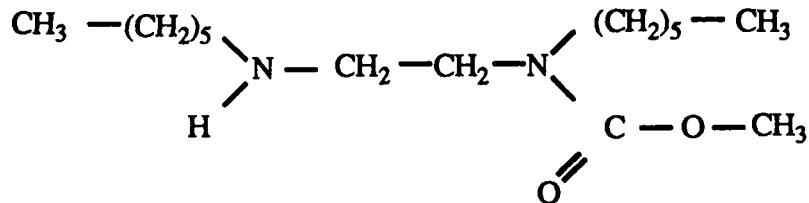
Test Substance

Chemical name: Methyl-N,N'-dihexylethylene diaminemonocarbamate (CHR4)

Molecular formula: C₁₆H₃₄N₂O₂

Source: SRI International
333 Ravenswood Avenue
Menlo Park, CA 94025

Structural formula:



Additional chemical information appears in Appendix A.

Vehicle

The vehicle for the CHR4 was corn oil (Mazola, Best Foods, CPC International, Englewood Cliffs, NJ).

Animal Data

Sprague-Dawley rats (Bantin-Kingman Inc, Fremont, CA) from a shipment received on 8 Jun 84 were used for this acute oral toxicity study. They were identified individually by ear tag. Two males and two females were selected randomly for quality control necropsy evaluation at receipt. Body weights of animals assigned to the study ranged from 97 g to 128 g on receipt. Additional animal data appear in Appendix B.

Husbandry

The rats were housed individually in stainless steel, wire mesh cages with automatically flushing dumptanks. The diet consisted of Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, Checkerboard Square, St. Louis, MO); water was provided by continuous drip from a central line. The temperature and relative humidity of the animal rooms were constantly monitored and maintained at 22° to 27°C and 27% to 54%, respectively. The photoperiod was 12 hours of light per day.

METHODS

Acclimation and Group Assignment

Eight males and eight females were assigned to each of six dose groups and five males and five females were assigned to the vehicle control group. Allocation was accomplished using a stratified, weight-biased method. Specifically, the animals were first ranked according to their body weight using the MINITAB statistical program on the Data General

Eclipse C/330 (LAIR SOP OP-STX-78). Group assignment was based on a random sequence of numbers generated by the RANDOM program on the C/330 (LAIR SOP OP-STX-21). The animals were acclimated for 20 days before dosing. During this period they were observed daily for any sign of illness.

Compound Preparation

Since CHR4 is an oily liquid immiscible with water. Therefore, it was diluted with corn oil to the 200 μ l/ml concentration used in the study. CHR4 is soluble in the corn oil and went into solution readily with stirring.

Dose Levels

The Approximate Lethal Dose (ALD) was determined to be between 220 and 300 μ l/kg for both male and female rats. Based on these data, test doses were selected (Table 1).

TABLE 1
CHR4 Dose Levels (μ l/kg)

<u>Males</u>	<u>Females</u>
192	178
222	206
256	238
296	275
342	318
396	368
vehicle	vehicle

Test Procedure

This study was conducted in accordance with EPA guidelines (5) and LAIR SOP-OP-STX-36 (6). Dosing was performed using the oral gavage method without animal sedation or anesthesia. Each animal received a volume of the dosing solution based upon the desired dose level and the animal's body weight. The volumes administered ranged from 0.20 to 0.49 ml for males and 0.14 to 0.35 ml for females depending on the animal's weight and dose group. Each male rat in the vehicle control group received 0.30 ml and each

female in the vehicle control group received 0.25 ml of corn oil. Sterile, disposable 1-ml syringes (Becton, Dickenson, & Co., Rutherford, NJ) fitted with 16-gauge, 3-inch ball-tipped feeding tubes (Popper & Sons, Inc., New Hyde Park, NY) were used for dosing. Dosing was conducted over 2 days, 26 and 27 Jun 84, in order to obtain a more accurate determination of the median lethal dose. Both males and females in the appropriate groups were dosed between 0800 and 1000 hours on both 26 and 27 Jun 84.

Observations

Observations for mortality and signs of acute toxicity were performed daily according to the following procedure: (a) animals were observed undisturbed in their cages, (b) animals were removed from their cages and given a physical examination, and (c) animals were observed after being returned to their cages. On the day of dosing, the animals were checked intermittently throughout the day. Observations were recorded at four and seven hours after dosing and daily for the remainder of the two-week observation period. A second "walk through" observation was performed daily with only significant observations recorded. Body weights were recorded weekly during the course of the study.

Necropsy

Animals that died during the 14-day test period were submitted for a complete gross necropsy. Those which survived the 14-day test period were submitted for necropsy immediately after termination by barbiturate overdose.

Statistical Analysis

Statistical analyses were performed on the mortality results. Selected lethal dose values were derived by probit analysis according to the maximum likelihood method, as described by Finney (7). The program, PROBIT, developed for the Data General Computer, Model C/330, was used to determine the probit curve and lethal dose values.

Duration of Study

Appendix C is a historical listing of study events.

Deviations from Protocol

This study was accomplished according to the protocol and applicable amendments with the following exceptions: (1) The number and size of dose groups were changed from five groups of 10 males and five groups of 10 females to six groups of eight males and six groups of eight females. This change was based on the ALD study results which suggested that CHR4 had a steep dose-response curve. The six dose groups permitted a more accurate description of the dose-response. (2) Due to a transcription error an ALD animal (84D01039) was inadvertently exchanged for animal 84D01031 from the male 342 μ l/kg dose group at necropsy following the 14-day observation period. This error was not detected until a routine review of animal dispositions. Since animal 84D01031 did not exhibit any clinical signs after the day of dosing and five other 14-day survivors that received this or higher doses were necropsied, the amount of information lost by failure to necropsy this animal was minimal. (3) To ensure dosing accuracy, the concentration rather than the volume administered was kept a constant. This was done because higher concentrations of CHR4 and corn oil were so viscous and the volumes to be administered would have been so small using our standard dosing procedures that dosing accuracy could not have been maintained. (4) The one and two hour recording of the clinical observations after dosing were deleted due to the length of the dosing procedure. It is the opinion of the investigators that the observations recorded at four and seven hours accurately reflected the clinical signs observed during the first hours after dosing. These changes did not appear to have any effect on the outcome or interpretation of the study results.

Storage of Raw Data and Report

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

RESULTSMortality

CHR4 produced lethality very rapidly as all 42 deaths occurred by 7.1 hours after dosing. In fact, 27 (64.3%) of these deaths occurred within 4 hours of dosing. Table 2 lists the compound-related deaths by group and the percent mortality. Appendix D is a tabular presentation of cumulative mortality.

TABLE 2
Test Compound-Related Deaths by Group

Dose Level (μ l/kg)	Deaths/ Number in Group	Percent Mortality
MALES		
192	2/8	25.0
222	1/8	12.5
256	3/8	37.5
296	4/8	50.0
342	6/8	75.0
396	6/8	75.0
Vehicle	0/5	0
FEMALES		
178	0/8	0
206	1/8	12.5
238	3/8	37.5
275	4/8	50.0
318	6/8	75.0
368	6/8	75.0
Vehicle	0/5	0

Lethal Dose Calculations

Lethal dose values were calculated by probit analysis, and the equation for the probit regression line was:
 $Y = -8.89 + 5.64 \log X$ for males and $Y = -15.39 + 8.34 \log X$ for females, where X is the dose and Y the corresponding probit value. Figures 1 and 2 graphically present the actual data points and the regression line. Lethal doses calculated from the equation for the probit regression line are presented in Table 3.

Figure 1
Dose Response Curve for CHR4 in Male Rats

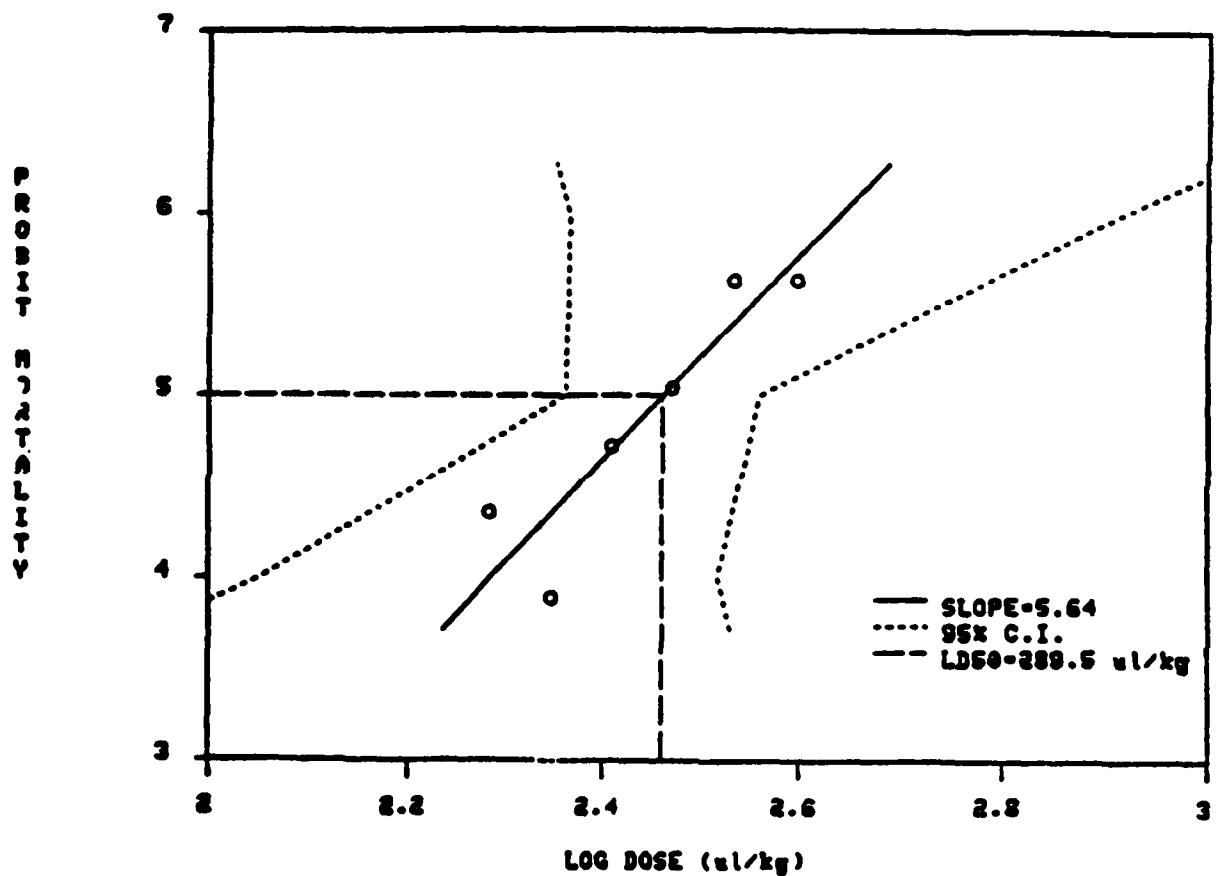


Figure 2
Dose Response Curve for CHR4 in Female Rats

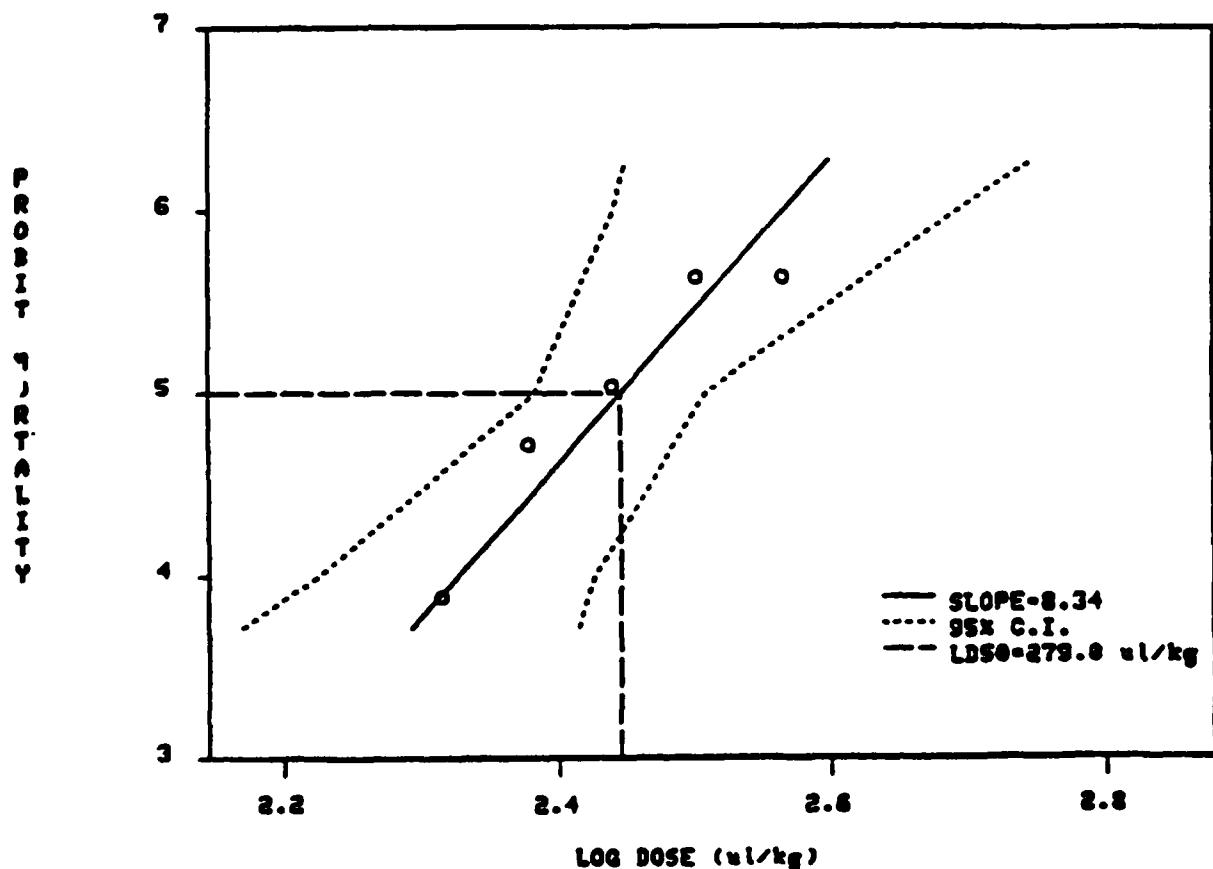


TABLE 3

Calculated Lethal Doses (LD) of CHR4

Effect Level	Calculated Dose (μ l/kg)	95% Confidence Limits (μ l/kg)
MALES		
LD16	193	(113, 330)
LD50	290	(230, 365)
LD90	488	(225, 1062)
FEMALES		
LD16	212	(168, 267)
LD50	279	(241, 323)
LD90	398	(282, 561)

Clinical Observations

Clinical signs produced by CHR4 were observed primarily on the day of dosing. By 24 hours after dosing observable responses had decreased dramatically and only occasional observations of clinical signs were noted thereafter. Because of the acutely occurring lethality following CHR4 administration, there were 25 animals (16 males and 9 females) that died before observations could be made. Although this represents more than 50% of the animals that died, there were sufficient clinical signs observed in the remaining animals to describe the clinical toxicity of CHR4 adequately. However, to provide an accurate description of the clinical sign occurrence, only the 71 animals (96 dosed minus the 25 that died before clinical signs could be recorded) for which signs had been recorded were used to describe the incidence of clinical sign occurrence.

The three most frequently observed signs or categories of signs observed following dosing with CHR4 were hunched posture (65 of 71), rough coat (58 of 71), and behavioral signs (55 of 71). Since rough coat (10 of 10), behavioral signs (irritability in 7 of 10), and hunched posture (6 of 10) were also observed with a high incidence in the control animals, these signs could be attributed to dosing with corn oil.

The other behavioral signs (inactivity, tremors, and hypotonia) plus the changes in reflexes (45 of 71), gastrointestinal signs (50 of 71), salivation (19 of 71), lacrimation (13 of 71), and convulsions (2 of 71) are attributable to administration of CHR4. Although these effects are obviously related to CHR4 administration, a dose-response relationship could not be established because of the acute lethality which precluded observation of clinical signs in many of the animals. Tables 4 and 5 contain summaries of the clinical signs observed in the male and female rats, respectively. Appendix E contains the individual animal histories.

Weight gains of the survivors were not affected by dosing. Table 6 presents the mean body weights by groups. Appendix F contains the individual body weights tables.

Pathology Report

Gastrointestinal hemorrhage and reddening (congestion or hemorrhage) in the lungs were the two findings observed in animals administered CHR4. These findings were dose-related as they were observed more frequently in the high dose groups. The pathology report is presented in Appendix G.

DISCUSSION

This study was conducted to evaluate and characterize the acute toxicity of CHR4 in the Sprague-Dawley rat. The calculated MLD for CHR4 was 290 μ l/kg in male and 279 μ l/kg in female rats. Based on a density of 0.9 g/ml for CHR4, these results represent MLD values of 261 mg/kg for male and 251 mg/kg for female rats. In accordance with the classification system of Hodge and Sterner (8), these MLD values place CHR4 in the "moderately toxic" category.

The spectrum of clinical signs observed in this study, diarrhea, salivation, lacrimation, muscle weakness, changes in reflexes, convulsions, and disorientation, and the rapid onset of the toxicity are consistent with the toxicity reported for other carbamate compounds (9). This toxicity is attributed to inhibition of cholinesterase enzymes resulting in an accumulation of excess acetylcholine at muscarinic, nicotinic, and central nervous system nerve terminals (10). Necropsy observations, which included gastric hemorrhage and pulmonary congestion, were also consistent with cholinesterase toxicity.

TABLE 4: Incidence Summary for Clinical Observations in Male Rats Administered CHR4

Category of Clinical Signs	Dose (μl/kg) N=	0	192	222	256	296	342	396
Behavioral ^a		5	4	4	4	3	4	5
Hunched Posture		4	7	7	5	4	2	5
Rough Coat		5	6	6	5	4	-	5
Stains ^b		1	-	2	3	3	-	-
Reflexes ^c		-	1	2	4	4	3	4
Stains, Perianal		-	2	3	3	3	3	2
Lacrimation		-	2	-	1	3	1	-
Salivation		-	-	2	1	1	1	2
Respiration ^d		-	-	2	-	2	1	-
Prostrate		-	-	-	-	-	2	-
Secretion, Penile		-	1	-	-	1	-	-
Death		-	2	1	3	4	6	6
Death with no Signs		-	1	1	3	4	4	3

^a Includes inactivity, tremors, irritability, disorientation, and hypotonia.

^b Includes reddish stains/material on mouth and nose.

^c Includes depressed grasping and righting reflexes

^d Includes rales, increased respiratory depth and rate.

**TABLE 5: Incidence Summary for Clinical Observations
in Female Rats Administered CHR4**

Category of Clinical Signs	Dose (µl/kg) N=	0	178	206	238	275	318	368
		5	8	8	8	8	8	8
Behavioral ^a		2	8	4	5	4	6	4
Hunched Posture		2	8	7	5	5	5	5
Rough Coat		5	8	6	5	4	4	5
Stains ^b		-	-	1	2	2	-	-
Reflexes ^c		-	8	2	6	3	5	3
Gastrointestinal ^d		-	7	7	5	5	5	5
Lacration		-	-	1	1	1	1	2
Salivation		-	1	2	2	2	4	1
Incr. Respiratory Rate		-	-	-	2	1	-	-
Prostrate		-	-	-	-	-	2	1
Convulsions		-	-	-	-	-	1	1
Death		-	-	1	3	4	6	6
Death with no Signs		-	-	1	2	3	1	2

^a Includes inactivity, tremors, irritability, disorientation, and hypotonia.

^b Includes reddish stains/material on mouth and nose.

^c Includes depressed grasping and increased startle reflexes

^d Includes perianal stains and diarrhea.

TABLE 6: Mean Body Weights in Grams \pm S.E. \dagger

Dose (μ l/kg)	Receipt	Dosing	Day 7	Day 14
MALES				
192	117.4 $\pm 3.6(8)$	237.8 $\pm 5.7(8)$	303.8 $\pm 8.1(6)$	309.0 $\pm 8.8(6)$
222	122.4 $\pm 1.3(8)$	229.9 $\pm 4.2(8)$	297.0 $\pm 8.2(7)$	296.1 $\pm 9.0(7)$
256	115.6 $\pm 2.9(8)$	225.5 $\pm 3.7(8)$	298.2 $\pm 5.4(5)$	300.6 $\pm 6.1(5)$
296	117.3 $\pm 3.2(8)$	224.3 $\pm 3.1(8)$	290.8 $\pm 12.1(4)$	295.8 $\pm 15.2(4)$
342	113.4 $\pm 2.8(8)$	235.5 $\pm 4.5(8)$	293.5 $\pm 5.5(2)$	315.0 $\pm 12.0(2)$
396	117.0 $\pm 2.4(8)$	235.5 $\pm 3.5(8)$	301.0 $\pm 1.0(2)$	304.0 $\pm 1.0(2)$
Vehicle	115.2 $\pm 3.6(5)$	221.8 $\pm 6.6(5)$	293.8 $\pm 7.8(5)$	293.6 $\pm 9.0(5)$
FEMALES				
178	112.0 $\pm 1.6(8)$	175.3 $\pm 4.2(8)$	215.9 $\pm 6.6(8)$	210.1 $\pm 6.1(8)$
206	111.6 $\pm 1.9(8)$	170.0 $\pm 4.0(8)$	214.7 $\pm 7.5(7)$	205.4 $\pm 5.9(7)$
238	110.61 $\pm 2.5(8)$	170.1 $\pm 4.5(8)$	215.4 $\pm 10.4(5)$	205.0 $\pm 10.9(5)$
275	114.9 $\pm 1.6(8)$	170.3 $\pm 4.2(8)$	212.3 $\pm 9.6(4)$	202.8 $\pm 9.5(4)$
318	113.5 $\pm 2.4(8)$	176.5 $\pm 3.7(8)$	212.5 $\pm 15.5(2)$	205.0 $\pm 16.0(2)$
368	115.0 $\pm 1.6(8)$	173.0 $\pm 4.5(8)$	203.0 $\pm 13.0(2)$	196.5 $\pm 18.5(2)$
Vehicle	113.6 $\pm 3.0(5)$	163.6 $\pm 4.7(5)$	200.2 $\pm 7.0(5)$	193.6 $\pm 6.2(5)$

 \dagger Number in parenthesis = number of animals.

CONCLUSIONS

CHR4 is a "moderately toxic" compound that produces characteristic signs of cholinesterase inhibition following oral administration. Calculated MLD values were 261 mg/kg (290 μ l/kg) in male and 251 mg/kg (279 μ l/kg) in female Sprague-Dawley rats.

REFERENCES

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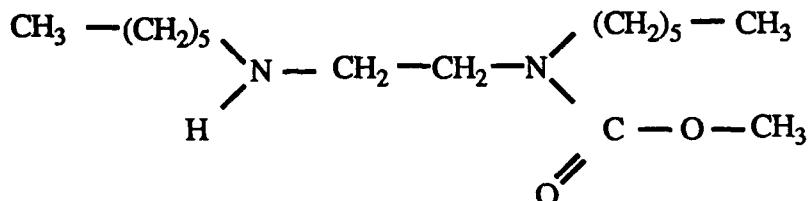
Appendix A: CHEMICAL DATA

Chemical Name: Methyl-N,N'-Dihexylethylene Diaminemonocarbamate

Other Names: CHR4, SRI 434-58

SRI Lot Number: 3K38075

Chemical Structure:



Molecular Formula: C₁₆H₃₄N₂O₂

Molecular Weight: 286.461

Physical State: Clear yellow liquid

Boiling Point: 146°C

pH: N/A Nonaqueous

Compound Density: 0.87 g/ml

Stability: Extremely stable at room temperature
(information provided by source)

Analytical Data/Purity: Infrared spectrophotometry was performed on 27 September 1983 at LAIR and was identical with an IR performed on 13 October 1982 at LAIR. Major bands in the IR spectrum were observed at 2930 (broad), 2860, 1705, 1475, 1405, 1200, 1100, and 775 cm⁻¹. Gas chromatographic analysis with FID detection indicated that 97.7% of the chromatographed material was CHR4.

Name of Contaminants and Percentages: Unknown

Source: SRI International
333 Ravenswood Avenue
Menlo Park, CA 94025

Appendix B: ANIMAL DATA

Species: *Rattus norvegicus*

Strain: Sprague-Dawley

Source: Bantin-Kingman
Fremont, CA

Sex: Male and Female

Date of Birth: Males: 30 April 1984
Females: 25 April 1984

Method of Randomization: Weight bias, stratified animal
allocation

Condition of animals at start of study: Normal

Body weight range at dosing: Males: 204 to 261 g
Females: 150 to 192 g

Identification Procedures: Ear tag.

Pretest conditioning: Quarantine/acclimation - 7 to 26 June 1984.

Justification: The laboratory rat has been proven to be a
sensitive and reliable model for lethal dose
determinations.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

<u>Date</u>	<u>Event</u>
7 Jun 84	Rats were received and individually caged.
8 Jun 84	Animals were checked for physical condition, sexed, weighed, and tagged. Five rats (2 males and 3 females) were submitted for necropsy quality control.
8-25 Jun 84	Animals were observed daily.
14-24 Jun 84	ALD animals were dosed.
20 Jun 84	Animals were weighed and randomized into dose groups.
25 Jun 84	Food was removed from animals in the Phase 1 dose groups at 1800 hours.
26 Jun 84	Phase 1 animals were weighed, dosed, and observed at approximately 4 and 7 hours after dosing. Food was removed from animals in the Phase 2 dose groups at 1800 hours.
27 Jun 84	Phase 2 animals were weighed, dosed, and observed at approximately 4 and 7 hours after dosing. Phase 1 animals were observed in am and pm.
27 Jun-11 Jul 84	All animals were observed daily for mortality and clinical signs in am and pm.
3 Jul 84	All animals were weighed.
10 Jul 84	All surviving Phase 1 animals were weighed and submitted for necropsy.
11 Jul 84	All surviving Phase 2 animals were weighed and submitted for necropsy.

Appendix E: INDIVIDUAL ANIMAL HISTORIES**MALES: Vehicle Control**

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00995	Hunched Posture Rough Coat Irritable	Jun 26 Jun 26 Jun 26, Jul 2	Slight Slight Moderate
84D01005	Hunched Posture Rough Coat Irritable	Jun 26 Jun 26, 27 Jun 26	Moderate Moderate Marked
84D01016	Rough Coat Irritable	Jun 26 Jun 26	Slight Marked
84D01022	Hunched Posture Rough Coat Irritable	Jun 26 Jun 26 Jun 26, 28, 29	Slight Slight Slight
84D01028	Hunched Posture Rough Coat Irritable Stain, Red, Nose	Jun 26 Jun 26, 27 Jun 26 Jun 26	Slight Moderate Marked Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

MALES: 192 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00982	Hunched Posture Rough Coat Irritable	Jun 27 Jun 27 Jun 27	Moderate Slight Slight
84D00985	Hunched Posture Rough Coat Stain, Perianal	Jun 27, 28 Jun 27, 28 Jun 27	Marked Moderate Marked
84D00998	Death	Jun 27	3.6 hr
84D01001	Hunched Posture Rough Coat	Jun 27 Jun 27	Moderate Slight
84D01010	Hunched Posture Rough Coat Tremors Stain, Perianal Lacrimation	Jun 27 Jun 27 Jun 27 Jun 27 Jun 27	Marked Moderate Slight Marked Slight
84D01017	Hunched Posture Irritable Lacrimation	Jun 27 Jun 27, Jul 4 Jun 27	Moderate Slight Moderate
84D01038	Hunched Posture Rough Coat Hypotonia Depr. Grasping Reflex Death	Jun 27 Jun 27 Jun 27 Jun 27 Jun 27	Moderate Slight Slight Slight 7.1 hr
84D01044	Hunched Posture Rough Coat Penile Secretion	Jun 27 Jun 27, Jul 4 Jun 27	Moderate Slight Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESMALES: 222 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00971	Hunched Posture Rough Coat	Jun 26, 27 Jun 26, 27, Jul 4	Marked Moderate
84D00975	Hunched Posture Rough Coat Stain, Perianal Salivation Stain, Red, Mouth Rales Stain, Red, Nose	Jun 26-28 Jun 26-29 Jun 26, 27 Jun 26 Jun 27 Jun 26, 27 Jun 30	Marked Moderate Marked Marked Moderate Present Slight
84D00977	Hunched Posture Rough Coat Irritable	Jun 26-28, 30 Jun 26, 28, 30 Jun 27, 28	Moderate Moderate Slight
84D00992	Hunched Posture Rough Coat Stain, Perianal Irritable	Jun 26, 27 Jun 26, 27 Jun 26 Jun 26, 28	Moderate Slight Slight Moderate
84D00994	Death	Jun 26	3.0 hr
84D01003	Hunched Posture Rough Coat Inactive Hypotonia Depr. Grasping Reflex Incr. Resp. Depth Stain, Perianal Salivation Stain, Red, Mouth	Jun 26, 27 Jun 26, 27 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26	Marked Marked Slight Moderate Moderate Moderate Slight Slight Slight
84D01017	Hunched Posture	Jun 26	Slight
84D01041	Hunched Posture Rough Coat Hypotonia Depr. Grasping Reflex	Jun 26, 27 Jun 26, 27 Jun 26 Jun 26	Moderate Slight Slight Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

MALES: 256 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00981	Hunched Posture	Jun 26	Slight
	Rough Coat	Jun 26, Jul 4	Slight
	Inactive	Jun 26	Slight
	Hypotonia	Jun 26	Moderate
	Depr. Grasping Reflex	Jun 26	Moderate
	Stain, Perianal	Jun 26	Moderate
	Irritable	Jun 26	Moderate
	Stain, Red, Mouth	Jun 26	Slight
84D00987	Death	Jun 26	6.0 hr
84D00989	Hunched Posture	Jun 26	Moderate
	Rough Coat	Jun 26	Moderate
	Hypotonia	Jun 26	Slight
	Depr. Grasping Reflex	Jun 26	Slight
84D01000	Hunched Posture	Jun 26, 27	Marked
	Rough Coat	Jun 26, 27	Moderate
	Irritable	Jun 26	Moderate
	Inactive	Jun 26	Moderate
	Hypotonia	Jun 26	Moderate
	Depr. Grasping Reflex	Jun 26	Marked
	Stain, Perianal	Jun 26	Marked
	Salivation	Jun 26	Marked
	Stain, Red, Mouth	Jun 26	Marked
	Lacrimation	Jun 26	Marked
84D01006	Death	Jun 26	3.1 hr
84D01020	Hunched Posture	Jun 26	Slight
	Rough Coat	Jun 26	Slight
84D01035	Death	Jun 26	3.1 hr

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESMALES: 256 μ l/kg CHR4 (cont.)

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01046	Hunched Posture	Jun 26	Moderate
	Rough Coat	Jun 26	Moderate
	Inactive	Jun 26	Moderate
	Hypotonia	Jun 26	Slight
	Depr. Grasping Reflex	Jun 26	Moderate
	Irritable	Jun 26-28	Marked
	Stain, Perianal	Jun 26	Marked
	Stain, Red, Mouth	Jun 26	Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESMALES: 296 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00980	Death	Jun 26	3.7 hr
84D00991	Death	Jun 26	3.0 hr
84D01008	Death	Jun 26	3.0 hr
84D01012	Hunched Posture Rough Coat Depr. Grasping Reflex Stain, Perianal Stain, Red, Mouth	Jun 26 Jun 26 Jun 26 Jun 26 Jun 26	Marked Slight Slight Moderate Slight
84D01021	Hunched Posture Rough Coat Inactive Hypotonia Incr. Resp. Rate Depr. Grasping Reflex Stain, Perianal Salivation Stain, Red, Mouth Lacrimation	Jun 26 Jun 26, 27 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26	Marked Moderate Slight Moderate Slight Marked Marked Moderate Moderate Moderate
84D01023	Death	Jun 26	3.7 hr
84D01026	Hunched Posture Rough Coat Inactive Hypotonia Depr. Grasping Reflex Depr. Righting Reflex Disoriented Lacrimation	Jun 26, 27 Jun 26, 27 Jun 26, 28 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26	Moderate Moderate Slight Marked Marked Slight Moderate Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESMALES: 296 μ l/kg CHR4 (cont.)

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01042	Hunched Posture	Jun 26-28	Marked
	Rough Coat	Jun 26-28, Jul 1	Marked
	Inactive	Jun 26, 27	Marked
	Hypotonia	Jun 26	Marked
	Depr. Grasping Reflex	Jun 26	Marked
	Stain, Perianal	Jun 26	Marked
	Salivation	Jun 26	Moderate
	Stain, Red, Mouth	Jun 26	Moderate
	Lacrimation	Jun 26	Moderate
	Penile Secretion	Jun 26	Slight
	Disoriented	Jun 26	Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

MALES: 342 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00996	Death	Jun 27	3.6 hr
84D00999	Hypotonia Depr. Grasping Reflex Stain, Perianal Salivation Prostrate Death	Jun 27 Jun 27 Jun 27 Jun 27 Jun 27 Jun 27	Marked Marked Marked Marked Present 7.0 hr
84D01014	Death	Jun 27	3.6 hr
84D01015	Hypotonia Depr. Grasping Reflex Prostrate Death	Jun 27 Jun 27 Jun 27 Jun 27	Marked Marked Present 7.0 hr
84D01024	Death	Jun 27	3.5 hr
84D01025	Death	Jun 27	3.5 hr
84D01027	Hunched Posture Inactive Stain, Perianal Rales	Jun 27 Jun 27 Jun 27 Jun 27, 28	Moderate Slight Marked Present
84D01031	Hunched Posture Inactive Hypotonia Depr. Grasping Reflex Stain, Perianal Lacration Disoriented	Jun 27 Jun 27 Jun 27 Jun 27 Jun 27 Jun 27 Jun 27	Marked Slight Moderate Slight Slight Slight Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

MALES: 396 µl/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D00979	Death	Jun 27	3.5 hr
84D00988	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Slight
	Hypotonia	Jun 27	Slight
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27, 28	Moderate
84D00993	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Moderate
	Inactive	Jun 27	Moderate
	Hypotonia	Jun 27	Slight
	Depr. Grasping Reflex	Jun 27	Slight
	Death	Jun 27	6.9 hr
84D01002	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27, 28	Moderate
	Inactive	Jun 27	Marked
	Tremors	Jun 27	Slight
	Hypotonia	Jun 27	Marked
	Depr. Grasping Reflex	Jun 27	Moderate
	Stain, Perianal	Jun 27	Marked
	Salivation	Jun 27	Slight
84D01004	Death	Jun 27	3.4 hr
84D01007	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Slight
	Tremors	Jun 27	Slight
	Death	Jun 27	6.8 hr
84D01029	Death	Jun 27	3.4 hr
84D01033	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Slight
	Inactive	Jun 27	Marked
	Hypotonia	Jun 27	Marked
	Depr. Grasping Reflex	Jun 27	Marked
	Salivation	Jun 27	Marked
	Death	Jun 27	6.8 hr

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES**FEMALES: Vehicle Control**

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01052	Rough Coat	Jun 26, Jul 4	Slight
84D01056	Rough Coat	Jun 26	Slight
84D01060	Hunched Posture Rough Coat Irritable	Jun 26 Jun 26 Jun 26	Slight Slight Marked
84D01085	Rough Coat	Jun 26	Slight
84D01122	Hunched Posture Rough Coat Irritable	Jun 26 Jun 26 Jun 26	Slight Slight Moderate

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALES: 178 µl/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01048	Hunched Posture	Jun 27	Moderate
	Rough Coat	Jun 27	Slight
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Marked
84D01051	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Moderate
	Inactive	Jun 27	Marked
	Disoriented	Jun 27	Slight
	Hypotonia	Jun 27	Marked
	Depr. Grasping Reflex	Jun 27	Marked
	Stain, Perianal	Jun 27	Marked
	Irritable	Jun 27	Moderate
84D01059	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Moderate
	Inactive	Jun 27	Moderate
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27	Moderate
84D01068	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Slight
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27	Slight
	Hypotonia	Jun 27	Slight
84D01071	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Moderate
	Inactive	Jun 27	Moderate
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27	Moderate
84D01077	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Slight
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27	Marked

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESFEMALES: 178 μ l/kg CHR4 (cont.)

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01084	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27, 28	Moderate
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27	Moderate
	Salivation	Jun 27	Moderate
84D01113	Hunched Posture	Jun 27	Moderate
	Rough Coat	Jun 27	Slight
	Hypotonia	Jun 27	Slight
	Depr. Grasping Reflex	Jun 27	Slight
	Stain, Perianal	Jun 27	Marked

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESFEMALES: 206 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01066	Hunched Posture	Jun 26	Slight
	Rough Coat	Jun 26	Slight
	Stain, Perianal	Jun 26	Moderate
84D01074	Hunched Posture	Jun 26	Marked
	Inactive	Jun 26	Slight
	Hypotonia	Jun 26	Moderate
	Depr. Grasping Reflex	Jun 26	Moderate
	Stain, Perianal	Jun 26	Marked
	Salivation	Jun 26	Marked
	Stain, Red, Mouth	Jun 26	Marked
	Lacrimation	Jun 26	Marked
84D01082	Hunched Posture	Jun 26	Marked
	Rough Coat	Jun 26	Slight
	Inactive	Jun 26	Slight
	Hypotonia	Jun 26	Slight
	Depr. Grasping Reflex	Jun 26	Slight
	Stain, Perianal	Jun 26	Slight
	Salivation	Jun 26	Slight
84D01090	Hunched Posture	Jun 26, 27	Slight
	Rough Coat	Jun 26	Slight
	Stain, Perianal	Jun 26	Moderate
84D01110	Hunched Posture	Jun 26	Moderate
	Rough Coat	Jun 26	Slight
	Stain, Perianal	Jun 26	Slight
84D01112	Hunched Posture	Jun 26	Slight
	Rough Coat	Jun 26	Slight
	Hypotonia	Jun 26	Slight
	Irritable	Jun 26	Slight
	Stain, Perianal	Jun 26	Moderate
84D01116	Hunched Posture	Jun 26	Slight
	Rough Coat	Jun 26	Slight
	Hypotonia	Jun 26	Slight
	Stain, Perianal	Jun 26	Slight
84D01119	Death	Jun 26	2.8 hr

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALES: 238 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01049	Death	Jun 26	2.8 hr
84D01055	Hunched Posture	Jun 26	Moderate
	Rough Coat	Jun 26, 27	Marked
	Hypotonia	Jun 26	Moderate
	Depr. Grasping Reflex	Jun 26	Moderate
	Stain, Perianal	Jun 26	Moderate
	Salivation	Jun 26	Moderate
	Stain, Red, Mouth	Jun 26	Slight
84D01057	Hunched Posture	Jun 26, 27	Marked
	Rough Coat	Jun 26	Slight
	Diarrhea	Jun 26	Slight
	Hypotonia	Jun 26, 27	Slight
	Depr. Grasping Reflex	Jun 26	Moderate
	Stain, Perianal	Jun 26	Marked
	Stain, Red, Mouth	Jun 26	Moderate
	Lacrimation	Jun 26	Slight
	Incr. Startle Reflex	Jun 27	Slight
84D01073	Hunched Posture	Jun 26, 27	Marked
	Rough Coat	Jun 26, 27	Moderate
	Inactive	Jun 26	Marked
	Hypotonia	Jun 26	Marked
	Depr. Grasping Reflex	Jun 26	Marked
	Incr. Resp. Rate	Jun 26	Moderate
	Stain, Perianal	Jun 26	Moderate
84D01087	Hunched Posture	Jun 26, 27	Moderate
	Rough Coat	Jun 26	Slight
84D01091	Hunched Posture	Jun 26	Marked
	Rough Coat	Jun 26	Slight
	Inactive	Jun 26	Slight
	Hypotonia	Jun 26	Slight
	Irritable	Jun 26	Slight
	Stain, Perianal	Jun 26	Moderate
	Depr. Grasping Reflex	Jun 26	Moderate
	Incr. Resp. Rate	Jun 26	Moderate

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES**FEMALES: 238 µl/kg CHR4 (cont.)**

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01105	Death	Jun 26	2.8 hr
84D01115	Inactive	Jun 26	Marked
	Salivation	Jun 26	Slight
	Depr. Grasping Reflex	Jun 26	Marked
	Hypotonia	Jun 26	Marked
	Stain, Perianal	Jun 26	Marked
	Death	Jun 26	5.2 hr

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALES: 275 µl/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01047	Hunched Posture Rough Coat Stain, Perianal Hypotonia Depr. Grasping Reflex Salivation Stain, Red, Mouth Lacrimation	Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26	Marked Slight Marked Moderate Moderate Moderate Moderate Slight
84D01064	Hunched Posture Rough Coat Depr. Grasping Reflex Stain, Perianal Irritable Stain, Red, Mouth	Jun 26 Jun 26, 27 Jun 26 Jun 26 Jun 26 Jun 26	Marked Moderate Slight Marked Slight Slight
84D01081	Death	Jun 26	2.8 hr
84D01097	Hunched Posture Rough Coat Inactive Tremors Hypotonia Depr. Grasping Reflex Incr. Resp. Rate Stain, Perianal Salivation	Jun 26 Jun 26-30 Jun 27 Jun 26 Jun 26 Jun 26 Jun 26 Jun 26, 27 Jun 26	Marked Marked Moderate Slight Marked Marked Moderate Marked Moderate
84D01098	Death	Jun 26	2.8 hr
84D01099	Hunched Posture Rough Coat Stain, Perianal Irritable	Jun 26 Jun 26, 27, 30 Jun 26 Jun 26	Moderate Slight Moderate Slight
84D01108	Death	Jun 26	2.7 hr
84D01117	Hunched Posture Stain, Perianal Death	Jun 26 Jun 26 Jun 26	Moderate Slight 5.9 hr

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALES: 318 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01050	Hypotonia	Jun 27	Marked
	Depr. Grasping Reflex	Jun 27	Marked
	Stain, Perianal	Jun 27	Moderate
	Prostrate	Jun 27	Present
	Death	Jun 27	6.7 hr
84D01054	Hunched Posture	Jun 27, 30, Jul 1, 4	Marked
	Rough Coat	Jun 27, 30, Jul 1, 4	Moderate
	Inactive	Jun 27	Moderate
	Disoriented	Jun 27	Slight
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Marked
	Stain, Perianal	Jun 27	Marked
	Salivation	Jun 27	Slight
	Irritable	Jun 27	Slight
84D01078	Salivation	Jun 27	Marked
	Convulsions	Jun 27	Present
	Prostrate	Jun 27	Present
	Death	Jun 27	3.3 hr
84D01093	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Marked
	Inactive	Jun 27	Marked
	Hypotonia	Jun 27	Marked
	Depr. Grasping Reflex	Jun 27	Marked
	Stain, Perianal	Jun 27	Marked
	Salivation	Jun 27	Marked
	Death	Jun 27	6.6 hr
84D01096	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27, 28	Slight
	Inactive	Jun 27	Slight
	Disoriented	Jun 27	Slight
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Moderate
	Stain, Perianal	Jun 27, 28	Moderate
	Irritable	Jul 4	Slight

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESFEMALES: 318 μ l/kg CHR4 (cont.)

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01102	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Slight
	Inactive	Jun 27	Moderate
	Disoriented	Jun 27	Slight
	Hypotonia	Jun 27	Marked
	Depr. Grasping Reflex	Jun 27	Marked
	Stain, Perianal	Jun 27	Marked
	Salivation	Jun 27	Moderate
	Death	Jun 27	3.2 hr
84D01106	Death	Jun 27	3.2 hr
84D01121	Hunched Posture	Jun 27	Slight
	Irritable	Jun 27	Slight
	Lacrimation	Jun 27	Slight
	Death	Jun 27	6.6 hr

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIESFEMALES: 368 μ l/kg CHR4

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01058	Salivation Convulsions Prostrate Death	Jun 27 Jun 27 Jun 27 Jun 27	Moderate Present Present 3.2 hr
84D01067	Hunched Posture Rough Coat Inactive Hypotonia Depr. Grasping Reflex Stain, Perianal	Jun 27, 28 Jun 27, 28 Jun 27 Jun 27 Jun 27 Jun 27, 28	Marked Moderate Marked Marked Moderate Moderate
84D01075	Hunched Posture Rough Coat Stain, Perianal Lacrimation Death	Jun 27 Jun 27 Jun 27 Jun 27 Jun 27	Moderate Slight Slight Slight 6.6 hr
84D01079	Death	Jun 27	3.2 hr
84D01083	Hunched Posture Rough Coat Tremors Hypotonia Stain, Perianal Death	Jun 27 Jun 27 Jun 27 Jun 27 Jun 27 Jun 27	Moderate Slight Slight Slight Slight 6.5 hr
84D01086	Hunched Posture Rough Coat Inactive Hypotonia Depr. Grasping Reflex Stain, Perianal	Jun 27, 28 Jun 27, 28 Jun 27 Jun 27 Jun 27 Jun 27	Marked Moderate Marked Marked Marked Marked

Appendix E (cont.): INDIVIDUAL ANIMAL HISTORIES

FEMALES: 368 μ l/kg CHR4 (cont.)

Animal Number	Clinical Signs	Dates Observed (1984)	Severity
84D01095	Hunched Posture	Jun 27	Marked
	Rough Coat	Jun 27	Moderate
	Hypotonia	Jun 27	Moderate
	Depr. Grasping Reflex	Jun 27	Moderate
	Stain, Perianal	Jun 27	Moderate
	Lacrimation	Jun 27	Marked
	Death	Jun 27	3.0 hr
84D01114	Death	Jun 27	3.1 hr

Appendix F: INDIVIDUAL BODY WEIGHTS**MALES: Vehicle Control**

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D00995	124	239	311	304
84D01005	116	204	273	264
84D01016	107	231	312	318
84D01022	107	209	291	294
84D01028	122	226	282	288
Mean	115.2	221.8	293.8	293.6
Standard Deviation	8.0	14.8	17.4	20.1
Standard Error	3.6	6.6	7.8	9.0

Appendix F (cont.): INDIVIDUAL BODY WEIGHTS

MALES: 192 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 6 (g)	Termination Day 14 (g)
84D00982	115	247	309	313
84D00985	125	231	279	284
84D00998	125	240	Death	
84D01001	111	225	284	287
84D01010	127	261	328	337
84D01017	115	248	322	329
84D01038	97	208	Death	
84D01044	124	242	301	304
Mean	117.4	237.8	303.8	309.0
Standard Deviation	10.1	16.2	19.8	21.6
Standard Error	3.6	5.7	8.1	8.8

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSMALES: 222 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D00971	123	245	318	328
84D00975	126	225	267	267
84D00977	119	211	282	282
84D00992	118	220	282	279
84D00994	120	231	Death	
84D01003	126	230	304	299
84D01019	120	247	328	328
84D01041	127	230	298	290
Mean	122.4	229.9	297.0	296.1
Standard Deviation	3.6	12.0	21.6	23.9
Standard Error	1.3	4.2	8.2	9.0

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSMALES: 256 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D00981	115	221	278	279
84D00987	113	223	Death	
84D00989	101	219	310	304
84D01000	121	231	298	297
84D01006	118	208	Death	
84D01020	108	225	300	309
84D01035	123	234	Death	
84D01046	126	243	305	314
Mean	115.6	225.5	298.2	300.6
Standard Deviation	8.2	10.6	12.2	13.6
Standard Error	2.9	3.7	5.4	6.1

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSMALES: 296 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D00980	105	208	Death	
84D00991	123	234	Death	
84D01008	119	220	Death	
84D01012	104	228	309	320
84D01021	113	236	314	324
84D01023	125	222	Death	
84D01026	121	221	273	272
84D01042	128	225	267	267
Mean	117.3	224.3	290.8	295.8
Standard Deviation	9.0	8.8	24.2	30.4
Standard Error	3.2	3.1	12.1	15.2

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSMALES: 342 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 6 (g)	Termination Day 14 (g)
84D00996	126	232	Death	
84D00999	123	244	Death	
84D01014	105	224	Death	
84D01015	111	261	Death	
84D01024	104	219	Death	
84D01025	115	236	Death	
84D01027	112	232	299	303
84D01031	111	236	288	327
Mean	113.4	235.5	293.5	315.0
Standard Deviation	7.8	12.8	7.8	17.0
Standard Error	2.8	4.5	5.5	12.0

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSMALES: 396 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 6 (g)	Termination Day 14 (g)
84D00979	106	228	Death	
84D00988	114	239	302	305
84D00993	125	246	Death	
84D01002	118	243	300	303
84D01004	123	245	Death	
84D01007	118	222	Death	
84D01029	123	239	Death	
84D01033	109	222	Death	
Mean	117.0	235.5	301.0	304.0
Standard Deviation	6.9	10.0	1.4	1.4
Standard Error	2.4	3.5	1.0	1.0

Appendix F (cont.): INDIVIDUAL BODY WEIGHTS

FEMALES: Vehicle Control

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D01052	114	176	216	211
84D01056	104	152	192	178
84D01060	115	160	195	181
84D01085	112	173	217	201
84D01122	123	157	181	197
Mean	113.6	163.6	200.2	193.6
Standard Deviation	6.8	10.4	15.8	13.9
Standard Error	3.0	4.7	7.0	6.2

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSFEMALES: 178 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 6 (g)	Termination Day 14 (g)
84D01048	114	153	177	174
84D01051	115	185	228	218
84D01059	110	176	208	218
84D01068	112	168	211	200
84D01071	111	167	217	205
84D01077	108	179	219	224
84D01084	120	187	239	228
84D01113	106	187	228	214
Mean	112.0	175.3	215.9	210.1
Standard Deviation	4.4	12.0	18.7	17.3
Standard Error	1.6	4.2	6.6	6.1

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSFEMALES: 206 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D01066	116	179	239	225
84D01074	118	184	238	220
84D01082	113	181	225	217
84D01090	110	173	215	205
84D01110	107	154	195	189
84D01112	107	155	196	186
84D01116	104	167	195	196
84D01119	118	167	Death	
Mean	111.6	170.0	214.7	205.4
Standard Deviation	5.4	11.4	19.9	15.6
Standard Error	1.9	4.0	7.5	5.9

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSFEMALES: 238 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D01049	123	173	Death	
84D01055	108	178	223	213
84D01057	114	171	217	200
84D01073	115	176	220	212
84D01087	102	150	177	167
84D01091	112	191	240	233
84D01105	104	162	Death	
84D01115	103	160	Death	
Mean	110.1	170.1	215.4	205.0
Standard Deviation	7.2	12.6	23.2	24.3
Standard Error	2.5	4.5	10.4	10.9

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSFEMALES: 275 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 7 (g)	Termination Day 14 (g)
84D01047	120	167	217	207
84D01064	117	172	222	211
84D01081	112	166	Death	
84D01097	109	150	184	175
84D01098	111	166	Death	
84D01099	120	183	226	218
84D01108	111	169	Death	
84D01117	119	189	Death	
Mean	114.9	170.3	212.3	202.8
Standard Deviation	4.6	11.8	19.2	19.1
Standard Error	1.6	4.2	9.6	9.5

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSFEMALES: 318 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 6 (g)	Termination Day 14 (g)
84D01050	117	172	Death	
84D01054	107	161	197	189
84D01078	122	178	Death	
84D01093	117	184	Death	
84D01096	114	184	228	221
84D01102	120	192	Death	
84D01106	107	176	Death	
84D01121	104	165	Death	
Mean	113.5	176.5	212.5	205.0
Standard Deviation	6.7	10.3	21.9	22.6
Standard Error	2.4	3.7	15.5	16.0

Appendix F (cont.): INDIVIDUAL BODY WEIGHTSFEMALES: 368 μ l/kg CHR4

Animal Number	At Receipt (g)	Dosing (g)	Day 6 (g)	Termination Day 14 (g)
84D01058	110	163	Death	
84D01067	117	156	190	178
84D01075	119	173	Death	
84D01079	106	158	Death	
84D01083	118	190	Death	
84D01086	116	178	216	215
84D01095	119	184	Death	
84D01114	115	182	Death	
Mean	115.0	173.0	203.0	196.5
Standard Deviation	4.7	12.7	18.4	26.2
Standard Error	1.6	4.5	13.0	18.5

Appendix G: PATHOLOGY REPORT

GLP Study 84023

Oral Lethal Dose (LD_{50})Substance: Methyl- α,β -Dihydroxyethylene Diaminomocarbamate (CHX4)Species: Rat Strain: Sprague-DawleyHistory: See LAIR SOP-OP-STX-36. Animals that did not die were killed with Sodium Pentobarbital anesthesia and axillary bleeding.Microscopic findings:

<u>Pachiology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Morphologic Diagnoses</u>
35782	84001042	Hemorrhage, peracute, multifocal, mild, lung; probable agonal event.
35808	84000985	Papilloma, skin, rat.

Gross Findings:

Treatment Group 1/male/222 ul per kg

<u>Pachiology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35763	84000971	Live - NR
35764	84000975	Live - NR
35765	84000977	Live - NR
35766	84000992	Live - NR
35774	84000994	dead - 3 hr* - NR
35771	84001003	Live - NR
35773	84001019	Live - NR
35781	84001041	Live - NR

*Time of death is rounded to the nearest 0.5 hr.

Appendix G (cont.): PATHOLOGY REPORT

Pathology Report
GLP Study 84023 (Cont)

Treatment Group 2/male/256 ul per kg

<u>Pathology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35766	84D00981	live - NR
35712	84D00987	dead - NR - 6 hr
35767	84D00989	live - NR
35770	84D01000	live - dilated right renal pelvis
35715	84D01006	dead - NR - 3 hr
35776	84D01020	live - stomach hemorrhage
35718	84D01035	dead - NR - 3 hr
35783	84D01046	live - NR

Treatment Group 3/male/296 ul per kg

<u>Pathology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35711	84D00980	dead - 4.0 hr - NR
35713	84D00991	dead - 3 hr - red lungs
35716	84D01008	dead - 3 hr - dilated renal pelvis
35773	84D01012	live - NR
35777	84D01021	live - NR
35717	84D01023	dead - 3.5 hr - NR
35779	84D01026	live - NR
35782	84D01042	live - red lung

Treatment Group 4/male/192 ul per kg

<u>Pathology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35807	84D00982	live - NR
35808	84D00985	Live - skin papilloma
35729	84D00998	dead - 4 hr - NR
35810	84D01001	Live - NR
35812	84D01010	Live - NR
35813	84D01017	Live - NR
35747	84D01038	dead - 7 hr - red lungs
35816	84D01044	Live - NR

Appendix G (cont.): PATHOLOGY REPORT

Pathology Report
GLP Study 84023 (Cont.)

Treatment Group 5/male/342 ul per kg

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35728	84000996	dead - 3.5 hr - NR
35743	84000999	dead - 7 hr - hemorrhage in small intestine
35731	84001014	dead - 3.5 hr - NR
35745	84001015	dead - 7 hr - hemorrhage in small intestine
35732	84001024	dead - 3.5 hr - NR
35733	84001025	dead - 3.5 hr - hemorrhage in small intestine
35814	84001027	Live - NR
None	84001031	Not received for necropsy

Treatment Group 6/male/396 ul per kg

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35727	84000979	dead - 3.5 hr - NR
35809	84000988	Live - NR
35742	84000993	dead - 7 hr - stomach hemorrhage
35811	84001002	Live - dilated right renal pelvis/red stomach mucosa
35730	84001004	dead - 3.5 hr - NR
35744	84001007	dead - 7 hr - red lungs
35734	84001029	dead - 3 hr - red lungs
35746	84001033	dead - 6.5 hr - red lungs/hemorrhage in small intestine

Treatment Group 8/male/vehicle

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35769	84000995	Live - NR
35772	84001005	Live - NR
35776	84001016	Live - NR
35778	84001022	Live - NR
35780	84001023	Live - NR

Appendix G (cont.): PATHOLOGY REPORT

Pathology Report
GLP Study 84023 (Cont)

Treatment Group 9/female/206 ul per kg

<u>Pathology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35791	84D01066	live - NR
35793	84D01074	live - NR
35794	84D01082	live - NR
35797	84D01090	live - NR
35801	84D01110	live - NR
35802	84D01112	live - NR
35803	84D01116	live - NR
35725	84D01119	dead - 3 hr - NR

Treatment Group 10/female/238 ul per kg

<u>Pathology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35719	84D01049	dead - 3 hr - NR
35786	84D01055	live - NR
35788	84D01057	live - NR
35792	84D01073	live - NR
35796	84D01087	live - NR
35798	84D01091	live - NR
35722	84D01105	dead - 3 hr - NR
35724	84D01115	dead - 3 hr - NR

Treatment Group 11/female/275 ul per kg

<u>Pathology</u> <u>Acc. No.</u>	<u>Animal</u> <u>ID No.</u>	<u>Gross Findings</u>
35784	84D01047	live - NR
35790	84D01064	live - NR
35720	84D01081	dead - 3 hr - NR
35799	84D01097	live - NR
35721	84D01098	dead - 3 hr - NR
35800	84D01099	live - NR
35723	84D01108	dead - 3 hr - NR
35726	84D01117	dead - 6 hr - NR

Appendix G (cont.): PATHOLOGY REPORT

Pathology Report
GLP Study 84023 (Cont)

Treatment Group 12/female/178 ul per kg

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35817	84D01048	live - NR
35818	84D01051	live - NR
35820	84D01059	live - NR
35822	84D01068	live - NR
35823	84D01071	live - NR
35824	84D01077	live - NR
35825	84D01084	live - NR
35828	84D01113	live - NR

Treatment Group 13/female/318 ul per kg

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35748	84D01050	dead 6.5 hr - NR
35819	84D01054	live - NR
35736	84D01078	dead - 3 hr - NR
35751	84D01093	dead - 6.5 hr - NR
35827	84D01096	live - NR
35739	84D01102	dead - 3 hr - NR
35740	84D01106	dead - 3 hr - NR
35752	84D01121	dead - 6.5 hr - NR

Treatment Group 14/female/368 ul per kg

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35735	84D01058	dead - 3 hr - NR
35821	84D01067	live - NR
35749	84D01075	dead - 6.5 hr - hemorrhage in small intestine
35737	84D01079	dead - 3 hr - NR
35750	84D01083	dead - 6.5 hr - red lungs
35826	84D01086	live - NR
35738	84D01095	dead - 3 hr - hemorrhage in small intestine
35741	84D01114	dead - 3 hr - NR

Appendix G (cont.): PATHOLOGY REPORT

Pathology Report
GLP Study 84023 (Coat)

Treatment Group 16/female/vehicle

<u>Pathology Acc. No.</u>	<u>Animal ID No.</u>	<u>Gross Findings</u>
35783	84001052	Live - NR
35787	84001056	Live - NR
35789	84001060	Live - NR
35795	84001085	Live - NR
35804	84001122	Live - NR

Table II
Summary Table - Males

<u>Group</u>	<u>Dose (ul/kg)</u>	<u>Number</u>	<u>Deaths</u>	<u>GI Hemorrhage</u>	<u>Lung Congestion</u>	<u>Time to Death</u>	
						3-5.5 hr	6-7 hr
8	0	5	0/5	0/5	0/5	0	0
4	192	8	2/8	0/8	1/8	1	1
1	222	8	1/8	0/8	0/8	1	0
2	256	8	3/8	1/8	0/8	2	1
3	296	8	4/8	0/8	2/8	4	0
5	342	7	6/7	3/7	0/7	4	2
6	396	8	6/8	3/8	3/8	3	3

Summary Table - Females

<u>Group</u>	<u>Dose (ul/kg)</u>	<u>Number</u>	<u>Deaths</u>	<u>GI Hemorrhage</u>	<u>Lung Congestion</u>	<u>Time to Death</u>	
						3-5.5 hr	6-7 hr
16	0	5	0/5	0/5	0/5	0	0
12	178	8	0/8	0/8	0/8	0	0
9	206	8	1/8	0/8	0/8	1	0
10	238	8	3/8	0/8	0/8	3	0
11	275	8	4/8	0/8	0/8	3	1
13	318	8	6/8	0/8	0/8	3	3
14	368	8	6/8	2/8	1/8	4	2

Appendix G (cont.): PATHOLOGY REPORT

Pathology Report
GLP Study 84023 (Cont.)

Comments:

1. Dose related toxicity of the compound is apparent.
2. Gastrointestinal hemorrhage and "reddening" (congestion and/or hemorrhage) of the lungs was observed in some animals in the higher dosage groups.
3. Most deaths occurred within 5.5 hours of dosing (29/42) and all occurred within 7 hours.



LANCE O. LOLLI NI, DVM
LTC, VC
Chief, Pathology Service Group

30 August 1984

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OFFICE OF NAVAL RESEARCH
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